Inherited Mouse Mutations as Models of Human Adnexal, Cornification, and Papulosquamous Dermatoses

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Nearly 100 mouse mutations have been described as causing some type of abnormality of the skin or hair. As only a few of these mutations have been studied in detail, they remain an untapped resource for furthering knowledge of basic cutaneous physiology and understanding the pathophysiology of analogous diseases in humans. Several diverse murine mutations are discussed. These include "asebia," a mildly hyperkeratotic disorder with sebaceous gland hypoplasia; "ichthyosis," an example of abnormal hair growth associated with hyperkeratosis; "rhino" and "hairless," two related examples of congenital follicular malformations; and "flaky skin", a potential animal model of eruptive psoriasis. *J Invest Dermatol 95:62S–63S, 1990*

Comparative dermatopathology is perhaps as old as the science of medicine itself. The word "alopecia," for example, is derived from the Greek word for fox ("alopex") apparently because many foxes at that time suffered from severe ectoparasite infestations. In the twentieth century, the value of rodent models in the basic and clinical sciences is well established. This is especially true for laboratory mice with genetically determined disorders. Large colonies of mutant mice can be easily maintained in a relatively small area and well-controlled manipulations can be performed. In addition, the mouse is the best-defined mammal in terms of molecular immunology and genomic characterization.

It is surprising, therefore, that with the notable exception of the NZB/NZW outcrosses that are used as a model of human lupus erythematosus, more murine models are not used as surrogates for investigating other human dermatoses. Nearly 100 mouse mutations with various forms of cutaneous abnormalities have been documented [1]. Most remain poorly defined or have yet to be characterized. In addition, new mutations commonly arise spontaneously in large production colonies or are induced by radiation, chemicals, or introduction of new genes (transgenic mice). In this report, a potpourri of these mutations are presented, including a recently discovered mutation that appears to closely resemble human psoriasis.

The "asebia" *(ab/ab)* mutation is autosomal recessive and fully penetrant, and maps to the distal end of mouse chromosome 19 [2]. The mice develop progressive alopecia and fine, mild epidermal scaling that becomes more severe with age [3]. The primary abnormality is hypoplasia of the sebaceous glands. There is also epidermal hyperplasia and mild dermal inflammation due to an increase in mast cells and macrophages that contain electron-lucent crystals that are apparently composed of lipid [4]. The rupture of the crystal-laden macrophages, which subsequently induces the release of a variety of inflammatory mediators and chemoattractants, has been proposed as the cause of epidermal hyperplasia [4].

The "ichthyosis" *(ic/ic)* mutant gene, which is located on mouse chromosome 1, has a phenotypic expression characterized by short, sparse, irregular hair shafts, and hyperkeratotic scales on the tail [5,6]. Microscopically, the major alteration is a non-scarring alopecia with mild epidermal hyperplasia and orthokeratosis. In 1960, Spearman [7] compared this mouse mutant to human ichthyosis vulgaris and psoriasis, postulating that increased epidermal turnover was the cause of the orthokeratosis. Later studies have demonstrated that in the "ichthyosis" mutant mouse, there is no increase in epidermal turnover rates [8].

The "hairless" *(hr/hr)* and "rhino" *(hr^{rh}/hr^{rh})* mutant mice are homozygous for autosomal recessive alleles located on mouse chromosome 14, the latter being a pathologically more severe cutaneous manifestation of "hairless." They have features similar to papular atrichia with alopecia in humans. The "hairless" mouse is commonly used in cutaneous absorption studies although its skin is far from normal. It is also used by some pharmaceutical manufacturers as a means of evaluating the effectiveness of antipsoriatic drugs by determining the time it takes promotor-induced epidermal hyperplasia of the ear skin to become normal after topical application of the antipsoriatic drug being investigated. Both "hairless" and "rhino" have generalized alopecia with prominent cystic and keratin plugged follicular infundibula (milia). These dilated structures often rupture and incite a severe foreign body inflammatory response [9]. The stable integration of a modified polytropic retrovirus has recently been determined to be the cause of the *hr* mutation [10]. Homozygotes (HRS/J-*hr/hr* mice) have a high frequency of lymphosarcoma compared to their littermate controls [9]. The "hairless" mice express selective defects in T-helper cell and macrophage functions [9].

The mutant mice described above represent either heritable animal skin diseases in search of a human model, or, as in the case of "hairless" and "rhino," a mouse mutation that resembles an extremely rare human disease. Recently, we have begun investigating a newly recognized mutant that may serve as an animal model for psoriasis.

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Identifying an animal model for psoriasis has been an important yet unsatisfied goal. Psoriasis is a disease that affects 1–2% of the population of the United States, yet it remains a disease for which there is no cure and factors responsible for its initiation, persistence, and resolution still remain speculative. Defining an animal model with spontaneous lesions that would give insight into this disease would provide a pivotal breakthrough for mechanistic studies. Of the two purported animal models of psoriasis described in the literature, both appear to be of limited value in a laboratory setting. Psoriasis has been reported in non-human primates, but only two cases have been identified [11,12]. A disease in pigs, porcine pustular psoriasiform dermatitis, is reported to have some features in common with human juvenile familial pustular psoriasis [13]; however, because the lesions regress after a period of three months and do not recur, the usefulness of this disease as an animal model for psoriasis is limited. Lengthy generation times for these animals, as well as the lack of specific antibodies against differentiation antigens and other species-specific reagents suggests that even if they were readily available, a thorough investigation of these diseases would be difficult [14].

In contrast, "flaky skin" *(fsn/fsn)*, a novel, autosomal recessive mutant, recently discovered in the A/J strain of mice, offers much promise as a research model for psoriasis. The mutation has pleiotropic effects involving the skin and hematopoeitic system [15]. Affected animals are clinically normal at birth, except for a hypochromic anemia. As the mutant mice age, they develop waxing and waning, focal to diffuse, grey-white, hyperkeratotic plaques. Microscopically, the lesions are characterized by dermal inflammation composed primarily of lymphocytes and macrophages associated with tortuous dermal blood vessels, epidermal hyperplasia with focal zones of neutrophilic exocytosis and profound hyperkeratosis composed of laminated orthokeratosis alternating with parakeratotic mounds containing neutrophils. This disease, therefore, has gross and microscopic features similar to human eruptive psoriasis. In addition, a positive Koebner reaction can be consistently elicited with tape stripping. Preliminary kinetics studies indicate there is approximately a tenfold increase in epidermal proliferation when compared to littermate controls. The features that this mouse mutation have in common with human psoriasis suggests that it may be of value as a model system for basic studies of the genetic, cellular, and physiologic basis of hyperkeratotic inflammatory skin diseases. At the present time, the *fsn* mutant gene is being inbred onto the BALB/cByJ and C57BL/6J backgrounds due to the poor fecundity of the mutants of the A/J background. Mapping of the mutant gene and more detailed evaluation of the mutant phenotype are in progress.

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